REMARKS

Claims 1-14 were pending in this application and have been cancelled without prejudice or disclaimer. New Claims 15-31 have been added. Support for the newly added claims may be found throughout the specification. For example, support for Claims 15-16 may be found at page 5, lines 19-27, page 6, lines 6-9 and lines 19-23, and pages 7-8, bridging paragraph; Claim 17 at page 6, lines 10-11; Claim 19 at page 6, lines 14-15; Claims 20-22 at page 7, lines 11-13; page 19, lines 26-34 and page 20, lines 1-5; Claims 23-26 at page 7, lines 3-10 and page 19, lines 26-34 and page 20, lines 1-15; Claim 27 at page 10, lines 9-28, page 18, lines 19-35 and page 19, lines 1-25; Claim 28 at page 10, lines 13-16; Claim 29-30 at page 7, lines 3-6, page 10, lines 9-28 and page 18, lines 19-35; and Claim 31 at page 10, lines 18 -19. Thus, no new matter is added by these amendments.

The amendments to the specification at pages 14 and 17 are being made to comply with the requirements for Sequence Listing Rules under 37 C.F. R. § 1.821-§ 1.825. The amendments assign sequence identifier numbers to sequences disclosed in the specification as required by 37 C.F.R. 1.821(d). Thus, no new matter is added by these amendments.

Reconsideration of the application in view of the following remarks is respectfully requested.

OBJECTIONS TO INFORMALITIES IN THE SPECIFICATION

The disclosure has been objected to as containing informalities because the specification contains handwritten alterations on pages 14 and 17 which have not been initialed and/or dated as required by 37 C.F.R. § 1.52 (c). As per the Examiner suggestion, Applicant has

amended the specification by deleting the handwritten notations on page 14 and 17 and substituting formal Sequence Identifier Numbers. Accordingly, Applicant respectfully requests withdrawal of this objection.

PRIORITY CLAIM

The Office Action states that the effective date for the claimed invention is the PCT (PCT/EP 97/05124) filing date of September 23, 1997 because applicant did not make a claim of priority in the declaration to the earlier filed Danish application (DK 1035/96 filed September 24, 1996). Applicant respectfully disagrees for the reasons presented below.

Applicant filed an executed four page Declaration (Exhibit A) concurrently with the U.S. National Application on March 23, 1999. The executed Declaration claimed priority to both PCT/EP 97/051241 (Exhibit A, page 1) and DK 1035/96 (Exhibit A, page 1). As evidenced by the attached return receipt postcard (Exhibit B), all four pages of the Declaration were received by the USPTO on March 23, 1999. As Applicant did claim priority to the Danish application (DK 1035/96) filed September 24, 1996 in the executed Declaration (Exhibit A), Applicant respectfully requests that the instant application be accorded a priority date of September 24, 1996 (the date of the Danish priority document).

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 9 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Cancellation of Claim 9 renders the Examiner's rejection with respect to that claim moot. New Claims 15-31 are believed to comply with the statute.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 9, 10, and 14 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Cancellation of Claims 9, 10 and 14 without prejudice or disclaimer render the Examiner's rejection with respect to those claims moot. Applicant traverses the rejection with respect to the newly presented claims for the reasons presented below.

One embodiment of the instantly claimed invention is directed to compositions comprising as a first component a vector capable of expressing via a T7 RNA polymerase promoter more than one DNA sequence encoding a Dengue virus antigen (selected from among the four serotypes of the Dengue virus) and as a second component a recombinant Modified Vaccinia Ankara (MVA) virus comprising a DNA sequence encoding T7 RNA polymerase. In addition, the instantly claimed invention provides methods of administering the aforementioned two component composition to initiate an immune response or vaccinate against Dengue virus infection. The Claims directed to the two component composition and methods of administering the two component composition were rejected by the Examiner because the Examiner contends the specification does not teach "...that both components are taken up by the same cells in a manner which produces an immune response effective to treat or prevent Dengue virus infection." (Office Action, page 3, 2nd paragraph). Applicant respectfully traverses this rejection for the reasons presented below.

The instant specification teaches how to administer the composition comprising two components, specifically a vector (e.g., a plasmid) expressing more than one Dengue virus serotype antigen under the transcriptional control of a T7 RNA polymerase promoter and a recombinant MVA virus expressing T7 RNA polymerase.(e.g., page 5, lines 19-27, page 7, lines 5-6; page 10, lines 13-28). The specification also teaches methods of administration of the two component composition to an animal (e.g., page 10, lines 13-28, page 20, lines 6-15). In addition, the specification teaches the timing of administration of the two components (e.g., administration of the plasmid containing more than one Dengue virus prior to the recombinant MVA-T7 polymerase) to optimize the expression of the antigen in cells (e.g., page 10, lines 13-28). Thus, the specification teaches how to make and use the claimed invention. It is well established that Applicants need not exemplify every claimed embodiment. In re Robins 429 F.2d 456, 456-457, 166 U.S.P.Q. 556, 555 (CFCA 1970).

Moreover, at the time of filing of the instant application the properties of the MVA virus had been demonstrated in clinical trials (page 5, lines 1-18) and MVA vaccines had been used for vaccination against smallpox (page 19, lines 28-34). An MVA virus expressing T7 polymerase was also known in the art (page 18, lines 19-35, page 19, lines 1-20). Thus, one of skill in the art would know how to make and use an MVA vaccine in conjunction with an MVA virus expressing a T7 polymerase. It is well established that Applicant need not teach what is known in the art. In re Howarth 654 F.2d 103, 210 U.S.P.Q. 689 (CCPA 1981).

Based on the foregoing arguments, Applicant submits that the instant disclosure provides quite sufficient information with respect to the administration of a vector expressing

more than one Dengue virus serotype antigen under the control of a T7 RNA polymerase promoter and a recombinant MVA virus expressing T7 RNA polymerase. Accordingly, Applicant respectfully submits that the Examiner has not met his burden of providing reasons or evidentiary support for the alleged non-enablement of the instant disclosure. In re Marzocchi, 439 F.2d 220; 169 U.S.P.Q. 367 (CFCA 1971). Applicant respectfully requests withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 3, 5, 6, 8 and 11 are rejected under 35 U.S.C. 103 (a) as being unpatentable over either Sutter et al. or Altenburger in view of Lai et al. Cancellation of Claims 1, 3, 5, 6, 8 and 11 render the Examiner's rejection with respect to those claims moot. Applicant traverses this ground of rejection with respect to the newly presented claims for the reasons discussed below.

The instantly claimed invention is based on a discovery by the Applicant that vaccination with a recombinant MVA virus expressing more than one Dengue virus serotype antigen (e.g., at least one antigen from two or more virus serotypes) results in immunity against all four serotypes of Dengue virus. Sutter et al. (C2) and Altenburger et al (U.S. 5,185,146) both relate to recombinant vaccinia vector sytem based on MVA and used to express proteins. Neither Sutter et al. or Altenburger teach or suggest the use of these recombinant systems to express more than one Dengue virus serotype antigen or the use of such systems to be used to provide immunity against all four Dengue virus serotypes.

Lai et al. (US 5,494,671) describes immunity in mice against Dengue virus serotype 4 after vaccination with a recombinant Vaccinia virus expressing antigens of Dengue virus serotype 4. Lai et al. therefore relates to a vaccine expressing only one Dengue virus serotype antigen which will provide immunity only against that particular Dengue virus serotype. Lai et al does not teach or suggest the use of a recombinant system to express more than one Dengue virus serotype antigen as a vaccine to provide immunity against all four Dengue virus serotypes. Thus Lai et al. either alone or in combination cannot render the claimed invention obvious.

Claim 4 is rejected under 35 U.S.C. 103 (a) as being unpatentable over either Sutter et al. (C2) or Altenburger in view of Lai et al. as applied to Claims 1, 3, 5, 6, 8, and 11 and further in view of Sutter (PNAS). Cancellation of Claim 4 renders the Examiner's rejection with respect to that claim moot. Applicant traverses this ground of rejection with respect to the newly presented claims for the reasons discussed below.

As discussed above, neither Sutter et al. (C2) or Altenburger render the claimed invention obvious. Sutter et al. (PNAS) relates to the use of recombinant MVA virus as a vector for heterologous gene expression. Sutter et al. (PNAS) does not teach or suggest the use of a recombinant MVA virus to express more than one Dengue virus serotype antigen, or that such a construct may be used as a vaccine to provide immunity against all four Dengue virus serotypes. Accordingly, Sutter et al does not remedy the deficiency of Sutter et al (C2) or Altenburger and cannot, either alone or in combination) render the claimed invention obvious.

Claim 7 is rejected under 35 U.S.C. 103 (a) as being unpatentable over either Sutter et al. or Altenburger in view of Lai et al. as applied to Claims 1, 3, 5, 6, 8, and 11 and further in view of Moss and either or both Hayes et al or Bancroft. Cancellation of Claim 7 renders the Examiner's rejection with respect to that claim moot. Applicant traverses this ground of rejection with respect to the newly presented claims for the reasons discussed below.

Moss is a general reference relating to the use of recombinant DNA virus vectors for vaccination. Hayes et al and Bancroft relates to the pathology of Dengue virus infection and the difficulties involved in developing a Dengue virus vaccine. Neither Moss, Hayes et al. or Bancroft either alone or in combination teach or suggest the use of a recombinant system to express more than one Dengue virus serotype antigen as a vaccine to provide immunity against all four Dengue virus serotypes. Accordingly, these references cannot render the claimed invention obvious.

Claim 9 is rejected under 35 U.S.C. 103 (a) as being unpatentable over either Sutter et al. or Wyatt et al. in view of Lai et al. Cancellation of Claim 9 renders the Examiner's rejection with respect to that claim moot. Applicant traverses this ground rejection with respect to the newly presented claims for the reasons discussed below.

Wyatt et al relates to the use of a recombinant MVA virus expressing T7 polymerase for transient gene expression in cells. Wyatt et al neither teaches or suggests the use of a recombinant system to express more than one Dengue virus serotype antigen or the use of such a construct as a vaccine to provide immunity against all four Dengue virus serotypes. As discussed above, neither Sutter et al. or Lai remedy this deficiency. Therefore, Wyatt et al

cannot render the claimed invention obvious. Withdrawal of this ground of rejection is respectfully requested.

In addition, Dengue virus outbreaks are a major public health concern in densely populated tropical and subtropical regions (page 2, lines 13-20). However, development of an efficacious and safe Dengue virus vaccine, as in the instant invention, has been complicated by the fact that the Dengue virus has four serotypes (types 1-4). Vaccination with one serotype provides protection only homotypic immunity. That is the vaccinated individual will only be immune to infection by the same serotype as used in the vaccine, but not immune to infection by the other three Dengue virus serotypes (page 2, lines 22-29). In addition, an individual immune to one Dengue virus serotype is at risk for a phenomena known as antibody-dependent enhancement (ADE) when infected with another Dengue virus serotype. In ADE the antibodies specific to the one serotype enhance the infectivity of another serotype resulting in a higher risk for developing a severe or fatal illness when infected with another serotype (page 2, lines 22-29). Based on this information, prior to Applicant's invention, the skilled artisan would have believed that infection with two or more Dengue virus serotypes would result in ADE. Thus, the prior art actually taught away from Applicant's claimed invention.

In fact, Applicant's discovery that vaccination with a recombinant MVA virus expressing more than one Dengue virus serotype antigen (e.g., at least one antigen from two or more virus serotypes) results in immunity against all four serotypes of Dengue virus without complications, such as ADE, was unexpected. Accordingly, the solution to the development of a

efficacious and safe Dengue virus vaccine is found only in the present disclosure. Thus, the cited references either alone or in combination cannot render the claimed invention obvious.

CONCLUSION

Applicants respectfully submit that the claims comply with 35 U.S.C. § 112, first and second paragraph and define an invention that is patentable over the art. Accordingly, allowance is in order, and an early notification to that effect would be appreciated. Should the Examiner in reviewing the communication have any questions or need any additional information, she is welcome to contact the undersigned at (650) 849-4902.

A fee of $890.00 (petition for 3 month extension) is believed due. The Assistant Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 50-1189. Docket No.: 20239-703. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

Dated: December 5, 2000

By: _____

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